IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091 Group Art Unit: 1618

Filing Date: May 6, 2005 Examiner: Gembeh, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

APPEAL BRIEF

James C. Lydon
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

Attorney for Appellants

TABLE OF CONTENTS **Page**

TABLE OF AUTHORITIES

Cases Page

Statutes

REAL PARTY IN INTEREST

An assignment of the invention claimed in this application from the inventors to Oy Juvantia Pharma Ltd., a Finnish corporation, is recorded in the U.S. Patent and Trademark microfilm records at Reel 17,238, Frame 0027. An assignment of the invention claimed in this application from Oy Juvantia Pharma Ltd. to Santhera Pharmaceuticals (Switzerland) Ltd., a Swiss corporation, is recorded at Reel 23,831, Frame 659. Accordingly, the real party in interest is Santhera Pharmaceuticals (Switzerland) Ltd.

RELATED APPEALS AND INTERFERENCES

A Notice of Appeal was filed January 10, 2011 in S.N. 10/534,117, "Improved Formulations Containing Substituted Imidazole Derivatives". Pending claims 1 and 3-18 define a fast-dispersing solid dosage form containing a substituted imidazole derivative of specified formula (I), The specific compound (fipamezole) whose claimed method of oromucosal administration is the subject of this appeal is encompassed within formula (I) of the '117 application's claim 1.

There are no other prior or pending appeals, interferences or judicial proceedings known to Appellants, the Appellants' legal representative, or Santhera Pharmaceuticals (Switzerland) Ltd. which

may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

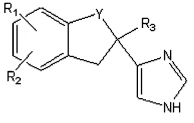
Claims 23 and 25-33 are pending, while claims 1-22 and 24 have been canceled. Each of pending claims 23 and 25-33 is being appealed from the rejections discussed below.

STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendments have been filed subsequent to the final rejection dated August 2, 2010. A Rule 132 declaration filed after the final rejection has been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

Substituted imidazoles of formula (I)

(I) 

where Y is $-CH_2-$ or -CO-, R_1 is halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, or an acid addition salt thereof, are highly selective and long-acting antagonists of α-

adrenoceptors. Fipamezole [4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole] is a specific example of such substituted imidazole compounds (Specification, page 1, lines 1-23), and is being developed for treatment of dyskinesia in Parkinson's Disease.

Claim 23 is the sole independent claim. The claimed method comprises oromucosally administering a formulation comprising fipamezole or its acid salt to a patient, wherein oromucosal administration is absorption via oral mucosa (Specification, page 2,lines 4-27).

The active ingredient of the oromucosal formulation may be a hydrochloride salt of fipamezole (Specification, page 3, lines 13-14).

The formulation may include at least one additive selected from the group consisting of solvents, preserving agents, flavoring agents and mixtures thereof. Suitable solvents include ethanol, water and mixtures thereof. Suitable preserving agents include methyl parahydroxybenzoate, propyl parahydroxybenzoate and mixtures thereof. The flavoring agent may be selected from the group consisting of aspartame, black currant and a mixture thereof (Specification, page 2, line 27 to page 3, line 3). Thus, an especially preferred formulation comprises (a) fipamezole or its

acid salt, (b) ethanol and water, (c) methyl parahydroxybenzoate and propyl parahydroxybenzoate, and (d) aspartame and black currant (Specification, page 3, lines 18-27).

The formulation may be oromucosally administered in the form of a spray, gel, a mucoadhesive buccal tablet or paste, or a sublingual tablet, and preferably in the form of a spray (Specification, page 3, lines 3-6). Examples 1-3 disclose illustrative spray formulations, Example 4 discloses an illustrative gel formulation, and Examples 5 and 6 disclose illustrative tablet formulations.

Oromucosal Administration Produces Improved Bioavailability of Fipamezole In Comparison to Oral Administration

Application Example 7 compares fipamezole plasma concentrations in healthy volunteers after 30 mg dose oral and oromucosal adiministration. The data show greater bioavailability after ormucosal tablet and spray administration in comparison to oral tablet administration. See Fig. 1 and Table 1 on page 8 of the application.

Oromucosal Administration Avoids QTc Prolongation, A Serious Side Effect Associated with Oral Administration of Fipamezole

The QT interval of an electrocardiogram (the time from the beginning of the QRS complex to the end of the T wave) is a measure

of the duration of ventricular depolarization and repolarization. QT interval is an important cardiac safety assessment because of its association with delayed ventricular repolarization and consequent risks for fatal arrhythmia (including *torsade de pointes*). The U.S. FDA has issued guidance to the pharmaceutical industry for its assessment.[1] A QT prolongation determination can require the abandonment of an otherwise promising drug candidate. Indeed, several drug have been withdrawn from the market due to cardiac safety concerns based on QT prolongation.[2]

Application Example 8 summarizes three animal studies evaluating the cardiac safety of fipamezole. The Appellants initially discovered that oral administration of fipamezole causes a dose-dependent prolongation of the QT interval in the dog (Specification, page 9, lines 5-10).

Surprisingly, however, the Appellants discovered that oromucosal administration of fipamezole does not prolong QT interval in the dog, despite the fact that oral administration prolongs the

---

[1]S7B "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" (U.S. Food and Drug Administration October 2005)(of record).

[2]Declaration of Dr. Jurg P. Seiler, Paragraph 9 and Appendix II, Executive Summary, first paragraph.

QT interval. Thus, Example 8 summarizes a toxicology study in which four male dogs were given fipamezole in buccal spray doses, with no QT prolongation being observed (Specification, page 9, lines 11-19). In another study, fipamezole was oromucosally administered to dogs (buccal administration at dose levels of 1, 5 and 10 mg/kg/day) for up to 4 weeks with no apparent QT prolongation (Specification, page 9, lines 20-23).

In short, the Appellants have discovered that a change of administration route (from oral administration to oromucosal administration) avoids a serious potential cardiac safety issue associated with fipamezole.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 23, 25-29 and 31-33 stand finally rejected under 35 U.S.C. § 103(a) over Huupponen et al., Clin.Pharmacol.Ther., 58, 506-11 (1995) in view of U.S. Patent No. 5,498,623 to Karjalainen et al.

2. Claims 23 and 25-33 stand finally rejected under 35 U.S.C. § 103(a) over Huupponen and Karjalainen, further in view of U.S. Patent No. 6,413,988 to de Proost.

These rejections are substantially similar, and Appellants appeal both rejections on the same grounds, discussed below.

ARGUMENT

The absence of a property which would be expected by those of ordinary skill in the art can overcome a *prima facie* case of obviousness. See, for example, Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 89 USPQ2d 1370 (Fed. Cir. 2008) (holding isolated stereoisomer non-obvious over racemic mixture in view of absolute stereoselectivity of claimed dextrorotary enantiomer which provides all of the desired antiplatelet activity and none of the adverse neurotoxicity), and In re May, 574 F.2d, 1082, 1090-94, 197 USPQ 601 (CCPA 1978)(holding isolated levo stereoisomer nonobvious over racemic mixture of stereoisomers, after conceded *prima facie* showing of obviousness, because isolated stereoisomer was unexpectedly non-addictive). The absence of QTc prolongation when fipamezole is oromucosally administered is such an unexpected and surprising property.

I. THE ABSENCE OF QTC PROLONGATION WHEN FIPAMEZOLE IS ORMUCOSALLY ADMINISTERED IS UNEXPECTED AND SURPRISING

The record demonstrates those of ordinary skill in the art would not expect a change of administration route to have any effect on a compound's QTc properties. Moreover, the record shows a compound's tendency to prolong the QTc interval cannot be predicted, particularly from heart rate data, and that fipamezole's QTc properties appear to be unique.

A. Those of Ordinary Skill Believe an Electrochemical Mechanism Is Responsible for QTc Prolongation

One of ordinary skill would not expect a change of administration route to significantly affect the QTc prolongation property of a compound. Instead, those of ordinary skill in the art believe the mechanism of QTc prolongation is linked to modification of the action potential, which is based on the balance between the inflow of positive ions (sodium and calcium) and the outflow of positive ions (potassium). See Crouch et al., "Clinical Relevance and Management of Drug-Related QT Interval Prolongation," 23 Pharmacotherapy 881 (2003)(of record) beginning at 882, right col., line 3. The most common mechanism of QT interval prolongation by drug molecules is believed to be inhibition of the potassium ion

current through the delayed rectifier potassium channel. International guidelines require pharmaceutical companies to test for a drug candidate's QT interval prolonging properties using the hERG assay to measure inhibition of the potassium ion current. See the Declaration of Dr. Jurg P. Seiler, Appendix II (Expert Statement), page 3, last line to page 4, line 12.

The Patent Office has failed to cite *any* evidence which shows that those of ordinary skill in the art believe a compound's QTc prolongation properties are different based on its mode of administration.

In short, the record demonstrates those of ordinary skill in the art believe the mechanism of QTc prolongation is based on electrochemical modification/inhibition of the potassium ion current. Once having learned that fipamezole can prolong QTc when orally administered, they would expect it to prolong QTc *regardless of its administration route* because the accepted mechanism of QTc prolongation involves electrochemical interaction between the pharmaceutical compound and cardiac tissue.

B. The Cited References Fail to Disclose Anything About QTc Prolongation

Huupponen, Karjalainen and de Proost all fail to disclose *anything* regarding QTc prolongation. None of these references disclose or suggest that oral administration of fipamezole can prolong QTc. None of these references disclose or suggest that oromucosal administration of fipamezole does not prolong QTc.

C. A Compound's Tendency to Prolong The QTc Interval Cannot be Predicted

The Patent Office now *concedes* those of ordinary skill in the art cannot predict a compound's tendency to prolong QTc based on a patient's heart rate (Second Advisory Action, page 2, lines 48-49). Instead, hERG assay and animal testing is required to determine whether a given compound will prolong QTc. Those of ordinary skill cannot predict a compound's tendency to prolong QTc, even in light of the properties of structurally similar compounds, because the interactions of compounds with the ion channels responsible for depolarization and repolarization events in cardiac tissue are very structure-specific. See paragraph 12 of Dr. Seiler's declaration.

The evidence of record demonstrates those of ordinary skill in the art would consider fipamezole's absence of QTc prolongation

when oromucosally administered to be unexpected and surprising in view of its tendency to prolong QTc when orally administered. First, the accepted QTc mechanism does not suggest that changing an administration route will affect QTc properties of a compound. Second, the cited references do not disclose or suggest changing an administration route will affect the QTc properties of fipamezole. Third, Dr. Seiler believes fipamezole's absence of QTc prolongation to be unexpected and surprising.[3] Dr. Seiler has further testified he is unaware of any other compound in which a change of administration route has eliminated QTc prolongation.[4]

In re Soini, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995) held an applicant's unsupported statement that his substantially improved results were unexpected was sufficient to establish unexpected results in the absence of evidence to the contrary. As discussed in detail above, the Appellants have provided evidence of the unexpected and surprising nature of fipamezole's absence of QTc prolongation when oromucosally administered. In stark contrast, the Patent Office has provided no evidence to the contrary. Instead, the Examiner has simply made an unsupported, conclusory statement

[3]Declaration of Dr. Jurg P. Seiler, paragraph 13.

[4]Id., paragraph 13, last sentence.

that the Appellants' discovery is not "truly unexpected" (Second Advisory Action, page 2, line 46).

Fipamezole's absence of QTc prolongation when oromucosally administered is unexpected and surprising, given its tendency to prolong QTc when orally administered, Sanofi-Synthelabo and May, supra. The Examiner's refusal to accept the Appellants' evidence of unexpected results is *reversible error* under Soini, supra.

II. APPELLANTS' SHOWING OF UNEXPECTED RESULTS IS COMMENSURATE IN SCOPE WITH THEIR CLAIMS

The dog toxicity studies summarized in Example 8 and discussed in detail in Dr. Savola's first declaration (filed February 17, 2009) fully support the claimed method. More specifically, an independent laboratory followed international guidelines on how to properly assess a drug's tendency to prolong the QT interval. These guidelines include the recording of electrocardiograms from dogs which have been administered the drug under investigation at various doses, including multiples of the anticipated human exposure to the drug. The data show oral administration of fipamezole causes QTc prolongation, with the prolongation increasing with increasing fipamezole plasma concentration once the systemic concentration in blood achieves a

certain threshold. The data also show oromucosal administration *of the same compound* does not prolong QTc at plasma concentrations equal to and greater than those which caused QTc prolongation upon oral administration.

A. The Examiner's Requirement That The Claims Recite The Absence Of QTc Prolongation Is Clearly Erroneous

The Examiner refuses to consider Appellants' unexpected results because "the claims do not recite the characteristics claimed" (Second Advisory Action, page 2, line 21).

It is hornbook law that a compound and all its properties are inseparable; they are one and the same thing under the patent law. See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Application Example 8 demonstrates fipamezole can prolong QTc when orally administered, but surprisingly does not prolong QTc when oromucosally administered. The sole independent claim requires oromucosal administration of fipamezole.

The Examiner's argument that the claims must recite fipamezole's properties is legal error, Papesch, supra. Her error is not harmless because she has refused to give any weight to Appellants' showing of unexpected results. In short, the Examiner's

argument that the claims must recite fipamezole's properties is *reversible error*.

B. The Examiner's Requirement That The Claims Recite A Dosage Amount Is Clearly Erroneous

Appellants' discovery concerns a novel administration route for fipamezole, in contrast to discovery of a critical, specific dosage amount or range. Accordingly, method claims 23 and 25-33 properly omit a dosage amount or concentration range.

It is hornbook law that a broad claim can be supported by a narrower range of data where one of ordinary skill in the art is able to ascertain a trend in the data which would allow him to reasonably extend the probative value of such data. In re Kollman, 595 F.2d 48, 201 USPQ 193 (CCPA 1979). In this case, one of ordinary skill would reasonably extrapolate the QTc data generated in the dog toxicity studies to the clinical situation based on the following facts:

1. Appellants' dog toxicity studies employed higher-than-clinical dosages, in accordance with international guidelines on how to assess a drug's tendency to prolong the QT interval.

2. These dog toxicity studies show that *oral* administration prolonged the QTc interval, with the prolongation increasing with increasing fipamezole plasma concentration once the systemic concentration in blood exceeds a certain threshold.

3. The dog toxicity studies also demonstrate *oromucosal* administration of fipamezole does not cause QTc prolongation at the same higher-than-clinical concentrations at which QTc prolongation had been observed upon *oral* administration.

Accordingly, one of ordinary skill would be able to ascertain a trend in the data (i.e., the dose dependent QTc prolongation effect of orally administered fipamezole) which would allow him to extend the probative value of such data to lower, clinical dosage amounts, Kolman, supra. More particularly, he would believe oromucosal administration of fipamezole would not prolong the QTc interval at *any* clinical dose in view of (1) the absence of QTc prolongation at higher-than-clinical dosages when oromucosally administered to the dog, and (2) the dose-dependent nature of QTc prolongation caused by *oral* administration of fipamezole in which greater amounts of fipamezole prolonged QTc longer than smaller

amounts of fipamezole. See paragraph Nos. 15-18 of Dr. Savola's second declaration, filed June 23, 2010.

The Examiner's argument that the claims must recite a fipamezole dosage amount or range is legal error, Kollman, supra. Her error is not harmless because she has refused to give any weight to Appellants' showing of unexpected results. In short, the Examiner's requirement that the claims recite a dosage amount or range is *reversible error*.

III. APPELLANTS HAVE COMPARED THE CLOSEST PRIOR ART

It is hornbook law that when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art. See Kao Corp. v. Unilever United States, Inc., 441 F.3d 963, 970, 78 USPQ2d 1257 (Fed. Cir. 2006). A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference, In re Merchant, 575 F.2d 865, 197 USPQ 785 (CCPA 1978).

The claimed method requires oromucosal administration of a single compound - fipamezole (or its acid salt).

U.S. Patent 5,498,623 to Karjalainen et al. discloses 4(5)-substituted imidazole derivatives, including fipamezole, their preparation and their use as an antagonist to α_2-adrenoceptors. Karjalainen teaches these derivatives may be administered orally, parenterally or intravenously, with oral administration preferred (Col. 4, lines 60-64). Fipamezole is specifically disclosed as compound No. 1 in Table 1 (Col. 2, lines 28-30). The *only* difference between the claimed method and Karjalainen et al. is the administration route of fipamezole.

In contrast, Huupponen et al., Clin.Pharmacol.Ther., 58, 506-11 (1995) is limited to atipamezole - a different imidazole compound. Huupponen teaches the oral bioavailability of atipamezole is poor, and discloses oromucosal administration improves atipamezole's bioavailability. *Nothing* is disclosed or suggested about any other imidazole compound.

U.S. Patent 6,413,988 to de Proost discloses an oral aqueous solution comprising prucalopride or pharmaceutically acceptable acid addition salts thereof. de Proost is cited to show preservatives

and sweeteners in pharmaceutical compositions, and fails to disclose or suggest oromucosal administration of fipamezole.

The Examiner argues Appellants have not compared the closest prior art (Second Advisory Action, page 2, lines 46-47). Apparently, in her view, Appellants should have compared fipamezole against atipamezole, a different compound than fipamezole. Yet Huupponen can hardly be more relevant to the claimed method of administration of fipamezole than Karjalainen, which expressly discloses oral administration of the same compound: fipamezole.

The CCPA in Merchant pointed out that a reference is not the closest prior art simply because it discloses a particular claim limitation:

> The board's approach appears to be that Pring is the "closest" prior art for what it shows, i.e., dry technique, and that, therefore, some sort of data comparing appellant's process with that of Pring should be forthcoming. That approach lacks a basis in law. To apply that approach would place a burden upon the applicant to provide comparison tests of his invention with every cited reference, for each reference may be said to be the "closest" prior art for the particular limitation it allegedly discloses.

Id. at 869 (Emphasis added). In short, the mere fact that Huupponen discloses oromucosal administration of a different compound than fipamezole does not make this reference the closest prior art.

The Merchant court went on to explain even the absence of a significant, patentability-imparting claim limitation from a reference does not necessarily diminish its status as the closest prior art:

> Nor would the absence of a significant limitation, such as "substantially anhydrous" here, from a reference necessarily diminish its position as the closest prior art. If the one limitation not disclosed in the closest reference be sufficient to render the claimed subject matter as a whole unobvious, the reference remains the closest (though not patentability-defeating) prior art.

Id. (Emphasis added). Thus, the absence of oromucosal administration from Karjalainen does not diminish its status as the closest prior art.

The Examiner's argument that oral administration of fipamezole is not the closest prior art to the claimed method of oromucosal administration of fipamezole is clearly erroneous, Merchant, supra. Moreover, her error is not harmless because she has refused to give any weight to Appellants' showing of unexpected results. In short, the Examiner's argument that oral administration of fipamezole is not the closest prior art is *reversible error*.

IV. THE EXAMINER HAS IMPROPERLY USED HINDSIGHT

It is error to use hindsight knowledge gleaned from the Appellants' specification as prior art:

> To imbue one of ordinary skill in the art with knowledge of the invention...when no prior art reference or references...convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

W.L. Gore and Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). See also KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007)("A factfinder should be aware...of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.")

The Examiner maintains her obviousness rejections - despite the weighty evidence of unexpected results discussed above - because fipamezole's administration route-dependent QTc properties are not "truly" surprising (Second Advisory Action, page 2, line 39). Yet both Huupponen and Karjalainen utterly fail to disclose or suggest that oral administration of fipamezole will prolong QTc, or that oromucosal administration of fipamezole will not prolong QTc. There is simply no disclosure whatsoever of QTc or QTc prolongation in either reference.

The *Appellants* discovered oral administration of fipamezole prolongs QTc. *They* subsequently discovered oromucosal administration of fipamezole does not prolong QTc. This information is disclosed *for the first time* in Appellants' specification.

The Patent Office improperly takes this knowledge - gleaned *entirely* from the Appellants' specification - to argue fipamezole's adminstration route-dependent QTc properties are not "truly unexpected". This is a classic case of *reversible error*, W.L. Gore, supra.

V. APPELLANTS' UNEXPECTED RESULTS OUTWEIGH ANY *PRIMA FACIE* CASE OF OBVIOUSNESS

Fipamezole's administration route-dependent QTc properties clearly overcome any *prima facie* case of obviousness raised by the combination of Huupponen and Karjalainen, as well as the combination of Huupponen, Karjalainen and de Proost. Appellants' surprising solution to fipamezole's QTc problem overcomes a serious side effect which can require abandonment of a drug candidate. Their discovery that oromucosal administration of fipamezole eliminates the QTc prolongation problem was not predictable, and goes against the conventional wisdom regarding the mechanism of QTc prolongation. Based on the totality of the circumstances, the claimed method of

oromucosal administration of fipamezole is patentable over the cited references.

CONCLUSION

It is hard to imagine a case with more persuasive unexpected results than this appeal. The uncontroverted evidence of record demonstrates (1) QTc prologation is a serious side effect which can require the abandonment of a drug candidate, (2) those skilled in the art believe the mechanism of QTc prolongation is an electrochemical inhibition of the potassium ion current associated with cardiac tissue repolarization, (3) fipamezole prolongs QTc when orally administered, but yet (4) inexplicably, oromucosal administration of the same compound does not prolong QTc. Fipamezole's administration route-dependent QTc properties outweigh any evidence of obviousness raised by the cited references.

The Examiner has committed reversible error by requiring the claims to recite both the absence of QTc prolongation and a dosage amount. She has erroneously used hindsight to discount fipamezole's administration route-dependent QTc properties as not "truly" unexpected.

Accordingly, this Board is respectfully requested to reverse both rejections of claims 23 and 25-33 and pass this application on to allowance.

Respectfully submitted,

/James C. Lydon/

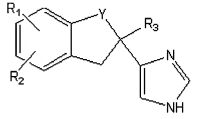
James C. Lydon
Reg. No. 30,082

Atty. Case No.: **TUR-168**
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone:(703) 838-0445
Facsimile:(703) 838-0447

CLAIMS APPENDIX

Claims 23 and 25-33

23. (Rejected) A method of administering a formulation comprising as an active ingredient a substituted imidazole of formula (I)

(I) 

where Y is $-CH_2-$ or -CO-, R_1 is halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, or an acid addition salt thereof, comprising

administering said formulation to a patient by oromucosal administration, wherein oromucosal administration is absorption via oral mucosa, and wherein said active ingredient is 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt.

25. (Rejected) The method of claim 23, wherein said active ingredient is a hydrochloride salt of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole.

26. (Rejected) The method of claim 23, wherein said formulation includes at least one additive selected from the group consisting of solvents, preserving agents, flavoring agents and mixtures thereof.

27. (Rejected) The method of claim 26, wherein the solvent is selected from the group consisting of ethanol, water and a mixture thereof.

28. (Rejected) The method of claim 26, wherein the preserving agent is selected from the group consisting of methyl parahydroxybenzoate, propyl parahydroxybenzoate and a mixture thereof.

29. (Rejected) The method of claim 26, wherein the flavoring agent is selected from the group consisting of aspartame, black currant and a mixture thereof.

30. (Rejected) The method of claim 23, wherein said formulation comprises the following components: (a) 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt, (b) ethanol and water, (c) methyl parahydroxybenzoate and propyl parahydroxybenzoate, and (d) aspartame and black currant.

31. (Rejected) The method of claim 23, wherein the formulation is administered in the form of a spray, gel, a mucoadhesive buccal tablet or paste, or a sublingual tablet.

32. (Rejected) The method of claim 31, wherein the formulation is administered in the form of a spray.

33. (Rejected) The method of claim 26, wherein said additive is a flavoring agent.

EVIDENCE APPENDIX

1. First Declaration Pursuant to 37 C.F.R. § 1.132 by Juha Savola Dated January 15, 2009

This evidence was filed February 17, 2009 together with an Amendment After Final Rejection and a Request for Continued Examination. Paragraph No. 9 of the Official Action mailed May 6, 2009 indicates the declaration was entered and considered by the Examiner.

2. Declaration Pursuant to 37 C.F.R. § 1.132 by Jurg P. Seiler

This evidence was filed December 30, 2009. Paragraph No. 8 of the Official Action dated February 25, 2010 indicates the declaration was entered and considered by the Examiner.

3. Second Declaration Pursuant to 37 C.F.R. § 1.132 by Juha-Matti Savola

This evidence was filed June 23, 2010. Paragraph No. 7 of the Official Action dated August 2, 2010 indicates the declaration was entered and considered by the Examiner.

4. Declaration Pursuant to 37 C.F.R. § 1.132 by Christian Funck-Brentano

This evidence was filed November 17, 2010. The penultimate paragraph of page 3 of the Second Second Advisory Action dated December 9, 2010 indicates the declaration was entered and considered by the Examiner.

5. S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (USFDA October 2005)

This evidence was filed as part of an Information Disclosure Statement on February 17, 2009. The Official Action mailed May 6, 2009 includes a copy of a Form PTO/SB/08b listing this evidence with the Examiner's initials indicating the evidence was entered and considered by the Examiner.

6. Crouch et al., "Clinical Relevance and Management of Drug-Related QT Interval Prolongation," 23 Pharmacotherapy 881 (2003)

This evidence was filed as part of an Information Disclosure Statement on February 17, 2009. The Official Action mailed May 6, 2009 includes a copy of a Form PTO/SB/08b listing this evidence with the Examiner's initials indicating the evidence was entered and considered by the Examiner.

7. Huupponen et al., Clin.Pharmacol.Ther., 58, 506-11 (1995)

This evidence was filed as part of an Information Disclosure Statement on May 6, 2005. The Official Action mailed March 8, 2007 includes a copy of a Form PTO-1449 listing this evidence together with the Examiner's initials indicating the evidence was entered and considered by the Examiner.

8. U.S. Patent 5,498,623 to Karjalainen et al.

This evidence was filed as part of an Information Disclosure Statement on May 6, 2005. The Official Action mailed March 8, 2007 includes a copy of a Form PTO-1449 listing this evidence together with the Examiner's initials indicating the evidence was entered and considered by the Examiner.

9. U.S. Patent 6,413,988 to de Proost

This evidence was listed in a Notice of References Cited attached to an Official Action mailed May 6, 2009.

10. FDA Center for Drug Evaluation and Research Standards Manual (January 11, 2006)

This evidence was filed as part of an Information Disclosure Statement on December 30, 2009. The Official Action mailed February 25, 2010 includes a copy of a Form PTO-1449 listing this evidence together with the Examiner's initials indicating the evidence was entered and considered by the Examiner.

RELATED PROCEEDINGS APPENDIX

1. S.N. 10/534,117, "Improved Formulations Containing Substituted Imidazole Derivatives"

A Notice of Appeal was filed January 10, 2011. No decisions have been rendered by the Board in this appeal.